UNITED STATES DISTRICT COURT
FOR THE
DISTRICT OF VERMONT

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| ETHEL KELLOGG,<br><br>Plaintiff,<br><br>v.<br><br>WYETH, Individually and as Successor-in-Interest to A.H. ROBINS COMPANY, INC. and AMERICAN HOME PRODUCTS CORPORATION; SCHWARZ PHARMA, INC.; ACTAVIS, INC.; ACTAVIS-ELIZABETH, L.L.C.; ALPHARMA, INC.; PUREPAC PHARMACEUTICAL COMPANY, INC.; TEVA PHARMACEUTICALS, USA, INC.; BAR PHARMACEUTICALS, INC.; PLIVA, INC.; and DRUG COMPANY DOES 1 THROUGH 10, inclusive,<br><br>Defendants. | : | Case No. 2:07-cv-82 |

**OPINION and ORDER**

Plaintiff Ethel Kellogg has sued defendants Wyeth, maker of Reglan, and several generic drug manufacturers of bioequivalent metoclopramide, the active ingredient in Reglan. Kellogg's second amended complaint alleges that the drug company defendants are liable for Kellogg's overexposure to metoclopramide, prescribed for treatment of gastroesophageal reflux disease ("GERD"). The complaint alleges that both Wyeth and the generic manufacturers were aware of the risk of long-term use of the drugs, yet took no steps to discourage the practice.

Several generic drug manufacturers seek dismissal of the complaint against them, arguing that Kellogg's claims are preempted by the Federal Food Drug & Cosmetic Act ("FDCA"), 21 U.S.C. § 301-399a, and its accompanying regulations. Before the

Court are Defendant Actavis-Elizabeth, L.L.C.'s ("Actavis") motion to dismiss the complaint under Rule 12(b)(6) (Doc. 29); Defendant Teva Pharmaceuticals USA, Inc.'s ("Teva") motion for judgment on the pleadings (Doc. 64); and Defendants Pliva, Inc. ("Pliva") and Barr Pharmaceuticals, Inc.'s ("Barr") motion to dismiss or for summary judgment (Doc. 67/70).

For the reasons that follow, the motions are **denied.**

## Background

For four years, from 2000 to June 2004, Kellogg took generic metoclopramide as prescribed as treatment for GERD. Prolonged use of metoclopramide, a neuroleptic or antipsychotic drug, can lead to tardive dyskinesia, a neurological disorder, and related extrapyramidal symptoms ("EPS"). EPS is a group of symptoms that may be side effects of antipsychotic medication, and include involuntary movements, tremors, rigidity, restlessness, muscle contractions and the like. According to her complaint, Kellogg's use of metoclopramide caused her to suffer a serious and permanent tardive dyskinesia syndrome, which includes oral dystonic facial grimacing, lip twisting, tongue thrusting, uncontrolled pronation of her feet, gait instability, difficulty swallowing and difficulty controlling her hands and arms.

Kellogg filed her complaint against Wyeth, manufacturer of Reglan, the name brand form of metoclopramide, and several manufacturers of generic metoclopramide. Of the eight counts in

her second amended complaint, five are products liability claims brought against all defendants, in which she asserts breach of a duty to exercise reasonable care in product labeling (Count Four); negligence per se in misbranding a prescription drug product (Count Five); strict products liability for failure to provide adequate warnings and instructions for the drug (Count Six); breach of express warranties for failure of the drug to conform to the defendants' representations (Count Seven); and breach of implied warranties since the drug was not fit for its common, ordinary and intended use in long-term therapy for GERD (Count Eight).

Essentially the generic drug manufacturers assert that because federal law requires them to label their product with exactly the same label as the one approved by the Food and Drug Administration ("FDA") for the name brand manufacturer, federal law preempts any state court tort claim based on failure-to-warn.

**I. Regulatory Framework**

The FDA is the federal agency charged with "protect[ing] the public health by ensuring that human . . . drugs are safe and effective." 21 U.S.C. § 393(b)(2)(B). To that end, the FDA regulates the introduction into interstate commerce of all new drugs. *Id.* § 355. In 1938, the FDCA established a system of premarket approval for drugs. *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 612 (1973); *see* Pub. L. No. 717, 52

Stat. 1040 (1938). Under the 1938 Act, a new drug could not be marketed unless it was shown to be safe for its intended use. *See Weinberger*, 412 U.S. at 612-13. The Drug Amendments of 1962 amended the FDCA to require that new drugs be both safe and effective for their intended use. *See id.*; Pub. L. No. 87-781, sec. 102(a)(1), 76 Stat. 780, 781 (1962).

In order to market a new drug one must file a New Drug Application ("NDA") with the FDA, which must include full reports of investigations into the drug's safety and effectiveness; a list of the drug's components; a full statement of the drug's composition; a description of the manufacturing methods, processing and packing; and "specimens of the labeling proposed to be used for such drug," among other things. 21 U.S.C. § 355(b)(1). The FDA must refuse to approve the NDA if it finds, among other things, that the reports of testing show that the drug is unsafe, fail to show that the drug is safe or are inadequate to show that the drug is safe; that the manufacturing methods are inadequate; that it has insufficient information to determine whether the drug is safe; that there is a lack of substantial evidence that the drug will have its intended effect; or "based on a fair evaluation of all material facts, [the] labeling is false or misleading in any particular." *Id.* § 355(d). It must withdraw approval of a new drug if it finds that the drug is unsafe, or there is a lack of substantial evidence

that the drug is effective. *Id.* § 355(e).

At the times relevant to this litigation,[1] the FDA required prescription drug labeling to "contain a summary of the essential scientific information needed for the safe and effective use of the drug," 21 C.F.R. § 201.56(a) (2004), as well as to include sections describing contraindications, warnings, precautions and adverse reactions. *Id.* § 201.57(d)-(g) (2004). A manufacturer was required to revise the labeling to include a warning "as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." *Id.* § 201.57(e) (2004).

The FDA also prescribed the procedure by which the labeling for a drug approved under an NDA could be changed to address new information about risks from the use of the drug. *See* 21 C.F.R. § 314.70(b)(3) (2004). Under § 314.70(c)(2)(i), a change in labeling "[t]o add or strengthen a contraindication, warning, precaution or adverse reaction" could be made before FDA approval by submitting a supplement to the FDA at the time the labeling is changed. *Id.*, § 314.70(c)(2)(i) (2004); *see also* Proposed Rule, New Drug and Antibiotic Regulations, 47 Fed. Reg. 46,622, 46,623,

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[1] Several regulations relevant to this case have been revised or redesignated after the time period during which Kellogg took metoclopramide. This opinion refers to the regulations in effect between 2000 and 2004, noting subsequent changes where applicable, unless the current regulation has remained unchanged.

46,635 (Oct. 19, 1982) (agency preclearance not required to effect changes to correct concerns about newly discovered risks from the use of the drug). Such a supplemental submission is known as a "Changes Being Effected," or "CBE" supplement.

The FDA maintains a public list of drugs which have been approved for safety and effectiveness under 21 U.S.C. § 355(c). *See* 21 U.S.C. § 355(j)(7). Drugs on this list are known as "listed drugs." *See id.*, § 355(j)(2)(A)(i). Once a listed drug loses patent protection, a company may seek permission from the FDA to market a generic version of the drug.

The Drug Price Competition and Patent Term Restoration Act of 1984 ("Hatch-Waxman Amendments") amended the FDCA to authorize an abbreviated new drug application ("ANDA") process for generic drugs that are bioequivalent to approved new drugs. *See* Pub. L. No. 98-417, sec. 101, 98 Stat. 1585 (codified at 21 U.S.C. § 355(j)). The legislation's purpose "was to increase competition in the drug industry by facilitating the approval of generic copies of drugs." *Mead Johnson Pharm. Group v. Bowen*, 838 F.2d 1332, 1333 (D.C. Cir. 1988). The Hatch-Waxman Amendments essentially adopted the FDA's procedure at the time for approving generic drugs. *See* Final Rule, Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950, 17,951 (Apr. 28, 1992).

An ANDA must include "information to show that the new drug is bioequivalent to the listed drug," 21 U.S.C. §

355(j)(2)(A)(iv), and "information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug," with limited exceptions. *Id.*, § 355(j)(2)(A)(v). The ANDA applicant is not required to conduct its own safety and effectiveness testing, but is permitted to rely upon the safety and effectiveness evidence presented in the NDA for the listed drug. *See SmithKline Beecham Consumer Healthcare, L.P. v. Watson Pharms., Inc.*, 211 F.3d 21, 26 (2d Cir. 2000); *Mead Johnson*, 838 F.2d at 1333.

In 1992, the FDA promulgated regulations to implement the Hatch-Waxman Amendments' ANDA requirements. Final Rule, Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950 (April 28, 1992). Title 21 C.F.R. § 314.94(a)(8) sets forth the labeling requirements for an ANDA, reiterating that labeling proposed for the generic must be essentially the same as the labeling approved for the reference listed drug. 21 C.F.R. § 314.94(a)(8)(iv) (2008). Examples of allowable differences in labeling include "differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act." *Id.*

The regulations provide that the FDA may withdraw approval

of an ANDA for a generic drug if it finds that the labeling for the generic drug "is no longer consistent with that for the listed drug." *Id.* § 314.150(b)(10). In commentary to the proposed regulations, FDA emphasized that it would not accept ANDAs for products with significant changes in labeling (such as new warnings or precautions) intended to address newly introduced safety or effectiveness problems not presented by the listed drug. *See* Proposed Rule, Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, 28,884 (July 10, 1989).

With regard to supplements and other changes to an approved ANDA, however, the regulations require an applicant to comply with the requirements of §§ 314.70 and 314.71 for NDAs. *Id.* § 314.97. The obligation to revise a label to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug applies to both generic and listed drug manufacturers. *See* 21 C.F.R. § 201.57(e) (2004) (generic drugs before June 30, 2006);[2] § 201.80(e) (2008) (generic drugs after June 30, 2006); § 201.57(c)(6)(i) (2008) (NDA drugs).[3]

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[2] Effective June 30, 2006, § 201.80(e) applies to older drugs such as metoclopramide. The regulation continues to require revision of the labeling "to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." 21 C.F.R. § 201.80(e) (2008).

[3] Congress's most recent amendments to the FDCA, in 2007, adopted requirements for postmarket studies and clinical trials, and enabled FDA to move more quickly to require NDA and ANDA holders to propose post-market labeling changes when the FDA

## II. Regulatory History of Metoclopramide

The FDA approved an NDA for Reglan and its labeling in 1980. Generic manufacturers began the ANDA approval process for generic metoclopramide beginning in 1986. The FDA approved metoclopramide as short-term (four to twelve weeks) therapy for adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy.

Kellogg alleges, however, that many doctors prescribed metoclopramide for much longer-term treatment of GERD. She claims that Wyeth actively promoted the idea that long-term use was both safe and effective, and that it and the generic manufacturers were aware of the widespread habit of prescribing for long-term use, but did nothing to discourage the practice. Second Am. Compl. ¶¶ 25, 35, 36; *see also McNeill v. Wyeth*, 462

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becomes aware of new safety information. *See* Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, title IX, 121 Stat. 823, 922 (2007) ("FDAAA"). The FDAAA includes a "rule of construction," which states that these new responsibilities "shall not be construed to affect the responsibility of the responsible person or the [ANDA holder] to maintain its label in accordance with existing requirements, including subpart B of part 201 and sections 314.70 and 601.12 of title 21, Code of Federal Regulations (or any successor regulations)." *Id.* 121 Stat. at 925-26. Subpart B's § 201.56(b)(2) makes ANDA holders subject to the labeling requirements of 21 C.F.R. § 201.80(e). That section provides that "labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." 21 C.F.R. § 201.80(e). Section 314.70's rules for changes to an approved application are applicable to ANDA holders. *See* 21 C.F.R. § 314.97.

F.3d 364, 369 (5th Cir. 2006) ("Wyeth was, or should have been, aware that Reglan was prescribed routinely for long-term use," given testimony that its own market data showed that 84% of patients were using Reglan long-term.). Eventually, in July 2004, after Kellogg had stopped taking metoclopramide, the FDA approved a request to add a sentence to the "Indications and Usage" section of the Reglan label: "Therapy should not exceed 12 weeks in duration."

Kellogg also alleges that the labeling for metoclopramide significantly understated the risk of experiencing EPS, despite mounting evidence that the risks of EPS in general and tardive dyskinesia in particular were much greater than represented, especially when patients took metoclopramide for extended periods. She asserts that the incidence of tardive dyskinesia in patients taking metoclopramide for six months or longer is as much as one in five, in stark contrast to the label's warning that one in five hundred patients may experience acute dystonic reactions, a type of EPS. No manufacturer proposed to the FDA that the label be changed to reflect this greater risk, nor took steps to alert health care professionals or patients to the risk. Kellogg asserts that FDA has never considered, much less rejected, a proposal to strengthen the warnings for the drug.

## Discussion

### I. Legal Standard

A court applies the same standard for motions to dismiss under Rule 12(b)(6) and for motions for judgment on the pleadings under Rule 12(c) of the Federal Rules of Civil Procedure, "'accepting the allegations contained in the complaint as true and drawing all reasonable inferences in favor of the nonmoving party.'" *Desiano v. Warner-Lambert & Co.*, 467 F.3d 85, 89 (2d Cir. 2006) (quoting *Burnette v. Carothers*, 192 F.3d 52, 56 (2d Cir. 1999)), *aff'd sub nom. Warner-Lambert Co., LLC v. Kent*, 128 S. Ct. 1168 (2008) (per curiam). Although Pliva and Barr have moved in the alternative for summary judgment, the Court declines to convert the motion, and will not consider factual matters outside the pleadings, other than matters of public record. *See* Fed. R. Civ. P. 12(d); *Global Network Commc'ns, Inc. v. City of New York*, 458 F.3d 150, 154-55 (2d Cir. 2006).

### II. Claims Not Based on Failure-to-Warn

At the outset, it is important to note that Kellogg's claims against the generic drug manufacturers are not exclusively based on failure to add to or strengthen the warnings in FDA-approved labeling for Reglan and generic metoclopramide, or to otherwise notify physicians about the risks of long-term use of the drug. A review of Kellogg's product liability claims demonstrates that Counts Four through Six do allege negligence, negligence per se

and strict products liability based on a failure to warn. In addition to claims based on failure to warn or inadequate labeling however, Count Seven asserts breach of express warranties, i.e., that the metoclopramide manufactured by the defendants failed to conform to the representations they made concerning its properties and effects; and Count Eight asserts breach of implied warranties, i.e., that the drug was not of merchantable quality or fit for its common, ordinary and intended use in long-term therapy for GERD. These claims are not based on failure to provide adequate warnings of the risks of long-term use of metoclopramide, and are not in any event preempted by the FDA's drug labeling regulations.

**III. Preemption**

The preemption doctrine arises from the Supremacy Clause of the Constitution, which provides that the "Constitution, and the Laws of the United States which shall be made in Pursuance thereof . . . shall be the supreme Law of the Land . . . any Thing in the Constitution or Laws of any State to the Contrary notwithstanding." U.S. Const. art. VI, cl. 2. This clause "invalidates state laws that "'interfere with, or are contrary to'" federal law. *Hillsborough County v. Automated Med. Labs., Inc.*, 471 U.S. 707, 712-13 (1985) (quoting *Gibbons v. Ogden*, 9 Wheat. 1, 211 (1824) (Marshall, C.J.)).

The United States Supreme Court recognizes three situations

in which state law may be preempted: "State action may be foreclosed by express language in a congressional enactment, by implication from the depth and breadth of a congressional scheme that occupies the legislative field, or by implication because of a conflict with a congressional enactment." *Lorillard Tobacco Co. v. Reilly*, 533 U.S. 525, 541 (2001) (citations omitted).[4] This case implicates only the third concept, conflict preemption.

**A. Presumption against preemption**

"[B]ecause the States are independent sovereigns in our federal system, . . . [i]n all preemption cases, and particularly in those in which Congress has 'legislated . . . in a field which the States have traditionally occupied,'" a court "'start[s] with the assumption that the historic police powers of the States [are] not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress.'" *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996) (quoting *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947)); *accord Altria Group, Inc. v. Good*, 555 U.S. ___, ___, No. 07-562, 2008 WL 5204477, at *4 (Dec. 15, 2008) ("When addressing questions of express or implied preemption, we begin our analysis with the assumption that the historic police powers of the States are not to be superseded by

[4] State law may include common law damages actions as well as statutes and regulations. *See Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 522 (1992). Moreover, "state laws can be preempted by federal regulations as well as by federal statutes." *Hillsborough County*, 471 U.S. at 713.

the Federal Act unless that was the clear and manifest purpose of Congress. That assumption applies with particular force when Congress has legislated in a field traditionally occupied by the States." (citation and internal quotation marks omitted)). States enjoy "historic primacy" to regulate matters of health and safety, which extends to the duties enforced by state tort claims. *Lohr*, 518 U.S. at 485; *see also Desiano*, 467 F.3d at 94-95, 98 (state tort law claims play an important role in state regulation of health and safety, applying presumption against preemption in case involving suit against drug manufacturing companies).

"The case for federal preemption is particularly weak where Congress has indicated its awareness of the operation of state law in a field of federal interest, and has nonetheless decided to 'stand by both concepts and to tolerate whatever tension there [is] between them.'" *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 166-67 (1989) (quoting *Silkwood v. Kerr-McGee Corp.*, 464 U.S. 238, 256 (1984)). Tort litigation against drug manufacturers has long coexisted with the FDCA and its numerous amendments. It is unlikely that Congress by its silence intended the Hatch-Waxman Amendments to accord generic drug manufacturers virtual immunity from tort liability. *See Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 449 (2005) ("The long history of tort litigation against manufacturers of poisonous substances

adds force to the basic presumption against pre-emption. If Congress had intended to deprive injured parties of a long available form of compensation, it surely would have expressed that intent more clearly."); *see also Desiano*, 467 F.3d at 95 & n.7 (finding no justification, in the absence of explicit expression of Congressional intent, for effectively gutting traditional state law duties between pharmaceutical companies and their consumers, noting that the presumption against preemption was at its strongest in such a case).[5]

To be sure, the presumption against preemption can be overcome. *See Riegel v. Medtronic, Inc.*, 451 F.3d 104, 123 (2d Cir. 2006) (recognizing presumption against preemption, but finding state tort claims preempted by express preemption provision of the Medical Device Amendments to the FDCA), *aff'd* 128 S. Ct. 999 (2008). The generic drug manufacturers do not dispute, however, that they must establish that it was the clear

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[5] In recent decisions finding failure-to-warn suits conflict-preempted, district courts have apparently declined to apply the presumption against preemption. *See Mensing v. Wyeth, Inc.*, 562 F. Supp. 2d 1056, 1061 (D. Minn. 2008); *Mason v. Smithkline Beecham Corp.*, 546 F. Supp. 618, 621-22 (D. Ill. 2008). Respectfully the Court disagrees with the suggestion that the presumption against preemption is not appropriate in such a case. It is precisely where Congress has not included an express statement concerning the preemptive effect of its enactment that courts must be mindful that they do not lightly tread on the historic powers of states to protect the health and welfare of their citizens, and apply the presumption. *See Colacicco v. Apotex Inc.*, 521 F.3d 253, 265 (majority op.), 276-77 (Ambro, J. dissenting) (3d Cir.), *petition for cert. filed*, 77 U.S.L.W. 3229 (U.S. Oct. 2, 2008) (No. 08-437).

and manifest purpose of Congress to preempt state law failure-to-warn claims. As frequently repeated, Congressional purpose "is the ultimate touchstone of preemption analysis." *Riegel v. Medtronic, Inc.*, 128 S. Ct. 999, 1013 (2008) (quoting *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 516 (1992)); *accord Lohr*, 518 U.S. at 485.

**B. Conflict preemption**

An actual conflict "arises when 'compliance with both federal and state regulations is a physical impossibility,' *Hillsborough County*, 471 U.S. at 713 (quoting *Fla. Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142-43 (1963)), or when state law 'stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress.'" *Id.* (quoting *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941)); *accord Sprietsma v. Mercury Marine*, 537 U.S. 51, 64-65 (2002).

The generic drug manufacturers contend that Kellogg's claims are preempted under both the impossibility and obstacle prongs of the conflict preemption doctrine.

**1. Impossibility conflict preemption**

Instances where it is impossible to comply with both federal and state law are rare, and courts have tended to offer examples rather than actual cases. *See Barnett Bank of Marion County, N.A. v. Nelson*, 517 U.S. 25, 31 (1996) (Impossibility conflict would exist "if the federal law said, 'you must sell insurance,'

while the state law said, 'you may not.'"); *Fla. Lime & Avocado Growers*, 373 U.S. at 143 (If federal orders forbade picking and marketing avocados with more than seven percent oil, and California excluded from the state any avocado with less than eight percent oil content, compliance with both requirements would be physically impossible.). The generic drug defendants are not faced with such a physical impossibility situation here.

The generic drug defendants argue that their labeling must always be identical to the listed drug, and a state common law damages action could result in requiring a warning that was not approved by the FDA. This could render the drug "misbranded," subjecting a manufacturer to penalties under the FDCA, or result in withdrawal of approval for the generic drug. There are two flaws in this argument. One, a plaintiff's judgment in a damages action does not require a drug manufacturer defendant to do anything with respect to its label. *See In re Zyprexa Prods. Liab. Litig.*, 489 F. Supp. 2d 230, 276-77 (E.D.N.Y. 2007) ("Jury verdicts do not impose mandatory labeling requirements on drug manufacturers; rather they impose damages for negligence in particular cases."). Two, should the FDA make a determination that a drug manufacturer, having responded to potential or actual tort claims with additional warnings on its label, had misbranded its drug, it must initiate an action in a federal district court in order to restrain a misbranding violation. *See* 21 U.S.C. §§

331, 332; *see also Perry v. Novartis Pharms. Corp.*, 456 F. Supp. 2d 678, 685 (E.D. Pa. 2006) ("FDA must initiate an enforcement action in order to find a drug misbranded"). There is no evidence that FDA has ever brought, or threatened to bring, an enforcement action against (or otherwise sanctioned) a drug manufacturer who sought to strengthen or add a warning to its label. Likewise, there is no evidence that FDA has proposed to withdraw approval for a generic drug because its manufacturer sought to strengthen a label warning. A hypothetical or potential conflict is insufficient to warrant preemption. *Rice v. Norman Williams Co.*, 458 U.S. 654, 659 (1982); *see also Witczak v. Pfizer, Inc.* 377 F. Supp. 2d 726, 731 (D. Minn. 2005) (declining to find irreconcilable conflict based on "assumptions of what the FDA would have done if defendant had unilaterally strengthened its warning label").

A jury's finding of liability or the threat of such a finding may persuade a drug manufacturer to change a drug's label, but it does not require it to do so. Common law rules, such as the ones at issue in Kellogg's suit, that require due care to communicate accurate and adequate information to physicians and patients, to avoid misbranding drugs, to refrain from marketing defective products, and to honor express and implied warranties do not "require[] that manufacturers label or package their products in any particular way." *Bates*, 544 U.S.

at 444. "[S]peculation as to whether a jury verdict would prompt a manufacturer to take any particular action (a question, in any event, that will depend on a variety of cost/benefit calculations best left to the manufacturer's accountants)" is not the proper inquiry. *Id.* at 445. A state tort judgment thus does not force a drug manufacturer to choose between violating federal or state law.

At the times relevant to this litigation, under the regulations then in force, a generic manufacturer having new information about the hazards of a drug could have availed itself of the CBE process, could have sought FDA approval for a change in the drug labeling, could have provided health care professionals with stronger warnings, or could have elected not to act and to accept the risk of tort liability should an injured plaintiff prevail on her suit. It was thus not physically impossible to comply with state and federal law.

**2. Obstacle conflict preemption**

State law is preempted when it "'stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress," whether the "obstacle" is described as "'conflicting; contrary to; . . . repugnance; difference; irreconcilablity; inconsistency; violation; curtailment; [or] interference.'" *Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 873 (2000) (quoting *Hines v. Davidowitz*, 312 U.S. at 67). There can

be no dispute that the core objective of the FDCA is to regulate the manufacture of drugs to ensure that they are safe and effective. *See, e.g., FDA v. Brown & Williamson Tobacco* Corp., 529 U.S. 120, 142 (2000).

The regulation of drugs has never been a strictly federal operation. In fact, the FDA's regulatory scheme has consistently relied on a role for state tort law. For example, in 1979, when the FDA adopted rules for labeling prescription drugs, it acknowledged that label information would lag behind medical knowledge, expected that manufacturers would make conservative medical judgments to protect themselves from civil liability, and disavowed any intention of protecting drug manufacturers from civil tort liability. *See* Final Rule, Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37,434, 37,434, 37,436-37 (June 26, 1979).

When Congress amended the FDCA in 1962, it included anti-preemption language: "Nothing in the Amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of State law." Drug Amendments of 1962, Pub. L. No. 87-781, sec. 202, 76 Stat. 780, 793 (1962). Although courts have differed on

the scope and the significance of this language, *compare Colacicco v. Apotex Inc.*, 521 F.3d 253, 262 n.8 (3d Cir.) ("[T]he plain language of this provision . . . merely states that conflict preemption applies."), *petition for cert. filed*, 77 U.S.L.W. 3229 (Oct. 2, 2008), *with Levine v. Wyeth*, 944 A.2d 179, 190-91 (Vt. 2006) (holding that the language essentially eliminates obstacle conflict preemption from consideration: "In other words, under any circumstances where it is possible to comply with both state law and the FDCA, the state law in question is consistent with the purposes and objectives of Congress."), *cert. granted* 128 S. Ct. 1118 (2008), there is no real dispute that Congress enacted the 1962 Amendments against a backdrop of state law, including state tort law.

There can likewise be no dispute that the Hatch-Waxman Amendments were intended to facilitate the availability of lower-cost generic drugs. *See, e.g., In re Tamoxifen Citrate Antitrust Litig.*, 466 F.3d 187, 191 (2d Cir. 2006). To that end, Congress allowed generic drug manufacturers to avoid duplicating clinical trials by requiring that the generic drug be bioequivalent to the listed drug, and that proposed labeling for a generic drug be virtually identical to that for the bioequivalent listed drug. *See* 21 U.S.C. § 355(j)(2)(A)(iv), (v). Nothing in the statute indicates that tort actions would henceforth stand as an obstacle to these Congressional objectives. Rather, the defendants argue

that jury verdicts would stand as an obstacle to the FDA's regulations, and its interpretation of them.

FDA drug labeling regulations have long been regarded as minimum standards of conduct. *See, e.g., Hill v. Searle Labs.*, 884 F.2d 1064, 1068 (8th Cir. 1989); *Wells v. Ortho Pharm. Corp.*, 788 F.2d 741, 746 (11th Cir. 1986); *In re Zyprexa Prods. Liab. Litig.*, 489 F. Supp. 2d at 274; *Jackson v. Pfizer, Inc.*, 432 F. Supp. 2d 964, 967 (D. Neb. 2006); *Witczak v. Pfizer, Inc.*, 377 F. Supp. 2d at 730-31; *Caraker v. Sandoz Pharms. Corp.*, 172 F. Supp. 2d 1018, 1033 (S.D. Ill. 2001); *Motus v. Pfizer, Inc.*, 127 F. Supp. 2d 1085, 1092 (C.D. Cal. 2000); *see also* Final Rule, Prescription Drug Product Labeling; Medication Guide Requirements, 63 Fed. Reg. 66378, 66384 (Dec. 1, 1998) ("FDA does not believe that the evolution of state tort law will cause the development of standards that would be at odds with the agency's regulations. FDA's regulations establish the minimal standards necessary, but were not intended to preclude the states from imposing additional labeling requirements. States may authorize additional labeling but they cannot reduce, alter, or eliminate FDA-required labeling."); Final Rule, 44 Fed. Reg. at 37,435 ("FDA recognizes that [prescription drug] labeling does not always contain the most current information available to physicians about the proper use of a drug.").

In 2006, however, in its preamble to a final rule amending

its drug labeling regulations, the FDA stated that its regulations with respect to the ANDA and NDA labeling requirements actually impose a federal ceiling as well as a floor, and that it "believes that . . . FDA approval of labeling under the [FDCA] . . . preempts conflicting or contrary State law." Final Rule, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006). It characterized its views on preemption as "long standing," and stated more particularly that it "believes that State laws conflict with and stand as an obstacle to achievement of the full objectives and purposes of Federal law when they purport to compel a firm to include in labeling or advertising a statement that FDA has considered and found scientifically unsubstantiated." *Id.* at 3934, 3935. Again, courts, and commentators, have differed on the scope and the significance of these and similar statements. *See, e.g.*, *Horne v. Novartis Pharms. Corp.*, 541 F. Supp. 2d 768, 780 (W.D.N.C. 2008) (collecting cases); Karen A. Jordan, *Agency Preemption and the* Shimer *Analysis: Unmasking Strategic Characterization by Agencies and Giving Effect to the Presumption Against Preemption*, 2008 Wis. L. Rev. 69, 102-03 (2008); James T. O'Reilly, *Losing Deference in the FDA's Second Century: Judicial Review, Politics, and a Diminished Legacy of Expertise*, 93 Cornell L. Rev. 939, 968-69 (2008); David C. Vladeck, *The FDA and*

*Deference Lost: A Self-Inflicted Wound or the Product of a Wounded Agency? A Response to Professor O'Reilly*, 93 Cornell L. Rev. 981, 982 (2008).

The Defendants argue that the FDA's position on preemption, as expressed in several amicus briefs as well as the preamble, is entitled to significant deference. As a panel of the Second Circuit Court of Appeals noted in *Desiano*, however, "it is not clear what, if any, deference would be owed to the FDA's view." *Desiano*, 467 F.3d at 97, n.9. It commented further: "whatever deference would be owed to an agency's view in contexts where a presumption against federal preemption does apply, an agency cannot supply, on Congress's behalf, the clear legislative statement of intent required to overcome the presumption against preemption." *Id.* at 98, n.9.

The *Chevron* doctrine recognizes "that considerable weight should be accorded to an executive department's construction of a statutory scheme it is entrusted to administer." *Chevron U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 844 (1984). *Chevron* deference, however, is "warranted only 'when it appears that Congress delegated authority to the agency generally to make rules carrying the force of law, and that the agency interpretation claiming deference was promulgated in the exercise of that authority.'" *Gonzales v. Oregon*, 546 U.S. 243, 915 (2006) (quoting *United States v. Mead Corp.*, 533 U.S. 218, 226-27

(2001)). "Otherwise, the interpretation is 'entitled to respect' only to the extent that it has the 'power to persuade.'" *Id.* (quoting *Skidmore v. Swift & Co.*, 323 U.S. 134, 140 (1944)).

Although the FDA has undoubted authority to engage in rule-making in connection with its responsibility to ensure drug safety and effectiveness, it does not appear to this Court that the agency's opinion on preemption of State law is "promulgated in the exercise of that authority." The agency's opinion appears in the preamble of its final rule on the content and format of prescription drug labels, and was not subject to the formal notice-and-comment process. *See* 21 C.F.R. § 10.85(d)(1) (a statement of policy or interpretation other than the text of a proposed or final regulation constitutes an advisory opinion). Congress has not delegated to the FDA any authority to preempt.

The weight of authority suggests that the FDA's opinion is at most entitled to *Skidmore* deference, its influence dependent "upon the thoroughness evident in its consideration, the validity of its reasoning, its consistency with earlier and later pronouncements, and all those factors which give it power to persuade." *Skidmore v. Swift & Co.*, 323 U.S. 134, 140 (1944).[6] *See Riegel*, 128 S. Ct. at 1009; *Lohr*, 518 U.S. at 505 (Breyer,

[6] The FDA itself has argued only that its views on preemption are entitled to "some weight" under *Skidmore*. *See* Brief for United States as Amicus Curiae at 26, *Wyeth v. Levine*, No. 06-1249 (U.S. June 2, 2008).

J., concurring) ("[I]n the absence of a clear congressional command as to pre-emption, courts may infer that the relevant administrative agency possesses a degree of leeway to determine which rules, regulation, or other administrative actions will have pre-emptive effect."); *Colacicco*, 521 F.3d at 274-75;[7] *accord In re Zyprexa Prods. Liab. Litig.*, 489 F. Supp. 2d at 273; *Knipe v. SmithKline Beecham*, ___ F. Supp. 2d ___, ___ , No. 06-3024, 2008 WL 4090995, at *16 (E.D. Pa. Aug. 28, 2008); Nina Mendelson, *Chevron and Preemption*, 102 Mich. L. Rev. 737, 789, 797-98 (2004).

Regardless of whether the FDA's current view on preemption is "long-standing," *see* Final Rule, 71 Fed. Reg. at 3934, or reflects a "seismic shift in FDA policy," *see* David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims*, 96 Geo. L.J. 461, 463 (2008), it addresses state laws that would compel a manufacturer to add to its labeling or advertising a statement that the FDA has considered and rejected. This comparatively narrow view of the preemptive scope of the labeling regulations may be persuasive if it develops that this case involves a warning that the FDA

[7] Although the district court in *Colacicco* concluded that the FDA's position was entitled to significant deference, *see Colacicco v. Apotex, Inc.*, 432 F. Supp. 2d 514, 525 (E.D. Pa. 2006), the Third Circuit panel concluded rather that the appropriate "level of deference approximat[ed] that set forth in *Skidmore*." *Colacicco*, 521 F.3d at 275.

considered and rejected. *See Lohr*, 518 U.S. at 505 (Breyer, J. concurring) (agency may possess leeway to determine which regulations have preemptive effect); *but see Desiano*, 467 F.3d at 97-98, n.9 (where presumption against preemption applies, agency cannot supply legislative intent to preempt). It has minimal relevance to the argument that the defendants advance here: that all failure-to-warn litigation against generic drug manufacturers is preempted. *See* Catherine M. Sharkey, *Products Liability Preemption: An Institutional Approach*, 76 Geo. Wash. L. Rev. 449, 519 (2008) (suggesting the preemption analysis focus on whether the FDA has considered and made a conclusive determination about the risk at issue); Mary J. Davis, *The Battle Over Implied Preemption: Products Liability and the FDA*, 48 B.C.L. Rev. 1089, 1148 (2007) ("The best argument for preemption in the prescription drug labeling context will be based on the FDA's specific consideration, and subsequent rejection of particular labeling proposed by a manufacturer that the FDA finds to be unsubstantiated based on the available data.").

The FDA's view recognizes that its regulation of drug labeling will not preempt all State law actions. *See* Final Rule, 71 Fed. Reg. at 3936. Taking the approach that a failure-to-warn claim based on information not previously submitted to the FDA is not preempted, the motions in this case must be denied. In their briefs the parties dispute whether FDA considered and rejected

warnings concerning the risks of long-term use of metoclopramide. Resolution of this issue requires factual determinations, inappropriate on motions to dismiss or for judgment on the pleadings. *Cf. Colacicco*, 521 F.3d at 268 (requiring review of the record of the FDA's treatment of the desired warning at issue before determining whether the state tort action based on failure to warn was preempted).

The pre-discovery posture of this case distinguishes it from the situation in *Wyeth v. Levine*, currently before the United States Supreme Court following affirmance of a jury verdict in favor of a migraine headache patient who suffered the amputation of her arm as a result of an injection of Wyeth's antinausea drug Phenergan. The Vermont Supreme Court affirmed, holding that Levine's state law claim for failure to warn was not preempted by FDA regulations. *Levine v. Wyeth*, 494 A.2d at 184. Wyeth had contended, in motions for summary judgment and for judgment as a matter of law following trial, that it had submitted a stronger warning of the risk of amputation as a result of inadvertent intra-arterial injection, but that the FDA rejected the change. *Id.* at 183; *see also id.* at 199 (Reiber, C.J., dissenting) (regulations arguably permit manufacturers to strengthen warnings for previously unknown and unanalyzed risks, not risks and benefits already evaluated by the FDA). In its briefs and argument before the United States Supreme Court, Wyeth and the

United States as amicus stressed repeatedly that the record before the Vermont superior and supreme courts demonstrated that the FDA was fully aware of the risk of this form of administration, yet chose not to require a strengthened warning in the approved label. *See* Brief for Petitioner at 3-4, 15-18, *Wyeth v. Levine*, No. 06-1249 (U.S. May 27, 2008); Brief for United States as Amicus Curiae at 4-5 (June 2, 2008); Tr. Oral Argument 5-6, 22-23 (Nov. 3, 2008). On the limited record in the case at bar this Court is unable to determine whether or to what extent any Defendant sought stronger warnings of the danger of prolonged use of metoclopramide, or whether the FDA considered and rejected stronger warnings.

The generic drug manufacturer defendants argue the broader position however, that failure-to-warn litigation in general threatens the FDA's authority to ensure that drugs are safe and effective and that their labeling is adequate and accurate. But such litigation does not necessarily interfere with the FDA's authority to approve labeling for NDAs and ANDAs. Failure-to-warn cases, such as this one, challenge drug manufacturers' failure to seek revisions to the approved labeling, or to otherwise warn physicians and their patients about risks that were not apparent, or were more severe than the applicant and the FDA knew at the time of approval. Moreover, failure-to-warn litigation does not seek to force manufacturers to change their

labeling, or to elevate a judge or jury's judgment over the FDA's; failure-to-warn litigation seeks compensation for injuries. *See* Kessler & Vladeck, 461, 476-477.

Title 21 C.F.R. § 314.70(c) sets forth the CBE procedure by which a drug manufacturer may change a label in order to add or strengthen a warning, in advance of FDA approval. The generic drug manufacturers argue that a generic drug's labeling must always be the same as the labeling for the reference listed drug, citing 21 U.S.C. § 355(j)(2)(A)(v) and (4)(G), and that § 314.70(c) does not apply to generic drug manufacturers. The defendants base their arguments on the FDA's stated position at the time it promulgated its final rule for ANDAs and statements in amicus briefs filed in other recent cases involving failure-to-warn claims.

In response to comments suggesting the ANDA applicants be permitted to deviate from the labeling for the reference listed drug to add contraindications, warnings, precautions, adverse reactions and other safety-related information, the FDA stated:

> the ANDA product's labeling must be the same as the listed drug product's labeling because the listed drug product is the basis for ANDA approval. Consistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart. If an ANDA applicant believes new safety information should be added to a product's labeling, it should contact FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised. After approval of an ANDA, if an ANDA holder believes that new safety information should be added, it should

> provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised.

Final Rule, Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950, 17,961 (Apr. 28, 1992). The regulations and the commentary do not address the generic manufacturer's duty under 21 C.F.R. § 201.80(e) (and former § 201.57(e)) to revise a label post-approval should it become aware of a significant risk.

The generic drug manufacturers argue that the FDA has interpreted its regulations to preclude them from adding warnings to approved labeling for a listed drug, and urge this Court to accord this view significant deference. An agency's interpretation of its own regulation is "controlling unless 'plainly erroneous or inconsistent with the regulation.'" *Auer v. Robbins*, 519 U.S. 452, 461 (1997) (quoting *Robertson v. Methow Valley Citizens Council*, 490 U.S. 332, 359 (1989)). *"Auer* deference is warranted only when the language of the regulation is ambiguous," however. *Christensen v. Harris County*, 529 U.S. 576, 588 (2000).

There is no ambiguity in the regulations at issue. Section 314.97 plainly instructs ANDA holders to comply with § 314.70 "regarding the submission of supplemental applications and other changes to an approved abbreviated application." If the FDA interprets this plain language nevertheless to carve out an exception for CBE changes to labeling, and reads the statutory

requirement that the ANDA application submit labeling identical to the listed drug as extending throughout the time the drug is marketed, the provision is plainly inconsistent with § 201.80(e) and former § 201.57(e). Title 21 C.F.R. § 201.80(e) requires that an ANDA holder revise its label whenever it becomes aware of an association of a serious hazard with the drug. To defer to FDA's interpretation "would be to permit the agency, under the guise of interpreting a regulation, to create *de facto* a new regulation," *Christensen*, 529 U.S. at 588, that would essentially eliminate any incentive for a generic drug manufacturer to ensure that its product continues to be safe and effective once it obtains its ANDA approval. Accordingly the Court does not defer to the FDA interpretation as argued by the defendants, as it is inconsistent with the unambiguous language of the regulations.

A state common law duty to warn of known risks does not present an obstacle to the federal regulatory duty to revise a drug label when its manufacturer becomes aware of a risk, or to provide physicians and patients with up-to-date warnings and precautions as long as the product is being marketed. State law failure-to-warn claims do not necessarily stand as an obstacle to the Congressional objectives of the FDCA or the Hatch-Waxman Amendments.

**Conclusion**

Applying the presumption against preemption, the generic

drug manufacturer defendants have not shown that Congress clearly intended to preempt all failure-to-warn litigation by requiring that ANDA applicants label their drugs identically to the reference listed drug. The motions to dismiss, for judgment on the pleadings or for summary judgment are hereby **denied.**

Dated at Burlington, in the District of Vermont, this 17th day of December, 2008.

/s/ William K. Sessions III
William K. Sessions III, Chief Judge
United States District Court